

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Autonomic Nervous System Function in Newborns with Congenital Heart Disease

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ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Abstract

Infants with complex congenital heart disease (CCHD) exhibit abnormal autonomic nervous system (ANS) function prenatally and are exposed to stressful environments postnatally that further alters autonomic development. Impaired autonomic function during early infancy influences behavioral, social, and cognitive development, and infants with CCHD are at high risk for developmental delays. The purpose of this study is to describe autonomic function during the perioperative period in newborns with CCHD and to explore associations with type of cardiac defect. In this multiple case study design, linear (power spectral density) and non-linear (Poincare plots) heart rate variability (HRV) were examined using four to 20 hour electrocardiographic recordings collected on four newborn infants with different types of CCHD. Data were collected during hospitalization once before surgery and once five to seven days after surgery. Hourly HRV was examined graphically, descriptively, with t-tests, and with Mann-Whitney tests. Graphical analyses suggested differences among infants in magnitude and trajectories of linear HRV power. Three infants (diagnosed with coarctation of the aorta, transposition of the great arteries, and double-outlet right ventricle) demonstrated significantly higher post-operative levels of linear HRV power compared with pre-operative levels. One infant (diagnosed with hypoplastic left heart syndrome) demonstrated reduced HRV post-operatively. Non-linear measures showed more abnormal Poincare plots post-operatively (11%-60%) than pre-operatively (0%-18%), revealing increased sympathetic activity following surgery in these infants. The infant with hypoplastic left heart syndrome showed the highest percentage of abnormal plots both pre- and post-operatively (18% and 60%, respectively). These findings revealed differences in linear and non-linear HRV by

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

cardiac defect. Additional studies with larger sample sizes and multiple longitudinal assessments are needed to enhance our understanding of relationships between specific cardiac defects and autonomic function. Knowledge about associations between early autonomic function and type of cardiac defect will assist with tailoring early interventions to optimize neurodevelopment in this vulnerable population.

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Chapter 1: Introduction

Complex congenital heart disease (CCHD) is responsible for cardiac dysfunction in 5 to 8 per 1000 live births. CCHD not only affects the cardiovascular system, but the rest of the body systems as well, such as the autonomic nervous system (Siddiqui et al., 2015). Early identification of the types of problems associated with CCHD could lead to early intervention, thus minimizing long-term disabilities. One of the problems known to occur in infants born with CCHD is abnormal neurodevelopment (Marino, 2012).

Evaluating the function of the autonomic nervous system (ANS), specifically the parasympathetic nervous system (PNS) using heart rate variability (HRV), may be a useful method of identifying early risk for neurodevelopmental delays. Research has shown that the PNS plays an important role in regulation of state, motor activity, and emotion (Calkins, 2007). Individual differences in ANS function may contribute to the expression and regulation of emotion and be key parts of displaying appropriate social behavior (Calkins, 2007). This study will identify the autonomic differences in infants hospitalized during the first weeks of life, many of them undergoing multiple surgeries.

The Autonomic Nervous system

The ANS, composed of the sympathetic nervous system (SNS) and the PNS, is mainly responsible for regulating physiological processes and helps to maintain ideal functioning in order for growth and development to occur (Pumpria, Howorka, Groves, Chester, & Nolan, 2002). The ANS is the involuntary portion of the nervous system responsible for regulating heartbeat and blood pressure, among other functions. Its role is to adjust these functions in order to maintain homeostasis. Homeostasis is balance in the body and its systems, and is primarily controlled by the parasympathetic nervous system

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

(Harrison & Brown, 2012). By maintaining this balance, the body can function optimally.

Heart Rate Variability

Autonomic nervous system function can be measured invasively or noninvasively by measuring changes in another organ as a representation for changes in ANS activity (Van Dijk et al., 2013). In the heart, function of the ANS can be reflected by changes in heart rate, specifically, changes in the intervals between heartbeats, which reflects interactions between the sympathetic and parasympathetic nervous systems (Harrison & Brown, 2012). The measure of intervals between each heartbeat is known as heart rate variability (HRV). The normal rhythm of the heart is controlled by the sinoatrial (SA) node, which receives input from the sympathetic and parasympathetic nervous systems. A branch of the vagus nerve innervates the SA node and when this branch is stimulated, a slower heart rate is produced. Decreased outflow from this nerve branch produces a faster heart rate (Porges, 1995). When the SA node is receiving less input from the PNS (also known as vagal withdrawal), the SNS takes over and the heart rate increases.

Congenital Heart Disease

Congenital heart disease mainly includes anatomic abnormalities present at birth, which result in impaired cardiac function. The cause of most CCHD is unknown, although genetic and environmental factors have been identified as possible causes. Congenital heart anomalies are often associated with chromosomal abnormalities, such as trisomy 21, commonly known as Down Syndrome (Hockenberry & Wilson, 2013).

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Neurodevelopment in CCHD

Children with CCHD are more likely to have neurodevelopmental difficulties than their healthy peers. The most frequent structural difference is microcephaly, a smaller than average head size usually due to abnormal brain development. Research has shown that developmental impairment in children with CCHD is characterized by cognitive delay in the first 2-3 years of life, as well as a lower than average intelligence quotient (IQ) (Martinez, 2013). Other neurodevelopmental differences include decreased performance in executive function (which includes focus and time management), language, and fine motor and visual-motor skills at school age with increased rates of psychosocial maladjustments and educational needs (Martinez, 2013). However, children with CCHD are not at an increased risk for major disabilities including cerebral palsy, severe intellectual disability, and significant hearing or visual loss (Martinez, 2013). Although the pathophysiology of this is not yet understood, researchers know that the extent of neurodevelopmental difficulties depends on the specific heart defect a child has (Martinez, 2013).

We studied infants with four different congenital heart defects including hypoplastic left heart syndrome (HLHS), transposition of the great arteries (TGA), coarctation of the aorta, and double-outlet right ventricle. While these heart defects are associated with many neurodevelopmental disabilities, some defects including ventricular septal defects (VSD) are associated with good neurodevelopmental outcomes, as long as no genetic abnormalities are present (Martinez, 2013).

Hypoplastic left heart syndrome (HLHS) is a heart defect with the most severe neurodevelopmental outcomes (Hockenberry & Wilson, 2013). HLHS occurs when the

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

left side of the heart is severely underdeveloped, thus affecting the blood flow to the body (Hockenberry & Wilson, 2013). Evaluation at 12 to 14 months shows notably lower scores on the Bayley Scales of Infant Development than healthy children (Hockenberry & Wilson, 2013). By school age, children with HLHS show higher rates of gross and fine motor dysfunction, and lower cognitive and adaptive behavior scores compared to children with other types of CCHD (Martinez, 2013).

Infants with TGA are born with their aorta and pulmonary artery reversed (Hockenberry & Wilson, 2013). Children with Transposition of the Great Arteries (TGA) often have motor disabilities, language disorders, decreased visual-spatial skills, and are at increased risk for behavioral problems, as well as increased behavioral dysfunction at school, and requiring more academic aid than their peers (Donofrio & Massaro, 2010).

In coarctation of the aorta, the descending aorta is narrowed, preventing optimal blood flow to the body. (Hockenberry & Wilson, 2013). This defect can lead to problems in adult-life including arterial hypertension, atherosclerotic disease, and the formation of aneurysms (Nguyen & Cook, 2015).

Double-outlet right ventricle occurs when the aorta and pulmonary artery both originate from the right ventricle. Infants with this defect are also born with a VSD, which is key to survival and allows blood to be shunted to the left side of the heart (Ceylan, 2014). Limited research is available about the long-term developmental deficits of children born with double-outlet right ventricle.

It is important to follow-up regularly with these children, as research shows that more than 50% of children with CCHD having normal developmental scores at their 1-year assessment have lower than average IQ's at 8 years of age (Martinez, 2013). In

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

CCHD it is common for children to also have an associated genetic syndrome, most commonly Down syndrome (Hockenberry & Wilson, 2013). These children with associated genetic syndromes are more at risk for neurodevelopmental delays (Martinez, 2013).

Neurodevelopment & ANS function in CCHD

Preoperative, fetal, and surgical factors have been found to result in a decreased heart rate and abnormal HRV, implying abnormal ANS function and potentially leading to neurodevelopmental issues (Siddiqui et al., 2015). Lower levels of HF arousal of the ANS as measured by HRV could be a fundamental feature of aggressive behavior in adults and adolescents (Aletti et al., 2012).

Putting It All Together

The functionality of the ANS can predict long-term neurodevelopment. In fact, fetal HRV is a significant predictor of child language competence and symbolic play during the third year of life (DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007). A higher HRV implies adaptability and well working autonomic control mechanisms, whereas a lower HRV implies inadequate adaptability of the autonomic control mechanisms (Harrison & Brown, 2012). High frequency HRV is a measure of parasympathetic activity (Harrison & Brown, 2012). Measuring changes in HRV can inform researchers of the status of an individual's ability to regulate physiologic processes. A higher variability indicates a better functioning autonomic nervous system (Harrison & Brown, 2012). Being able to identify these autonomic differences early in a child's life supports the need for interventions to enhance these ANS functions in children with CCHD.

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Chapter II: Literature Review

Neonates with CCHD are often hospitalized and undergo surgery in the first weeks and months of life for an extended period of time. Consequently, these infants experience a high stress state for long periods, which leads to an increase in SNS activation (Harrison & Brown, 2012). The high stress environment of an intensive care unit can lead to cognitive, social, emotional, behavioral, and motor delays (Daniels & Harrison, 2015). One case study measured noise level, exposure to light, and sleep in an infant with TGA who had undergone surgery shortly after birth (Daniels & Harrison, 2015). The level of noise this infant was exposed to on the second, third, and fourth days of the study exceeded the appropriate recommended amount, and the levels of light exposure exceeded the recommendation by 2.2 times (Daniels & Harrison, 2015). Researchers also found that this infant was aroused from sleep between 66 and 102 times daily for the four-day period of data collection, and sleep duration was less than 30 minutes at a time. This is important because sleep is a key component in brain development of a newborn. This study describes the environment an infant with CCHD is placed in early in life (Daniels & Harrison, 2015). More study is needed to identify associations with the infant's development.

Although not much is known about ANS function in children with CCHD, sympathetic stimulation and parasympathetic inhibition has been linked to cardiac disease in adults (Florea & Cohn, 2014). One study demonstrated that adults with coronary artery disease undergoing coronary bypass surgery have a lower HRV, meaning they have a reduced capability of regulating physiologic functions and processes, leading to many physiological issues, including increased ventricular stiffness (Florea & Cohn, 2014).

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Several studies have shown the differences in autonomic nervous system function in children with a congenital heart defect compared to healthy children without any heart defects. One study found that baseline HRV was significantly higher in healthy infants at 2 weeks of age compared to infants with Transposition of the Great Arteries (TGA) (Harrison & Ferree, 2014). The study hypothesized that interaction with the mother has a direct effect on the development on ANS function. Interaction with mother can aid infant arousal through stimulation of the sympathetic and parasympathetic pathways, allowing the ANS to be developed and refined (Harrison & Ferree, 2014). Infants with TGA are often hospitalized in intensive care units shortly after birth; therefore their interaction with mother is scarce, limiting the opportunity of their autonomic nervous system to become as developed as a healthy infant's. ANS was measured by high frequency (HF) HRV, which is closely related with the ability to regulate social and emotional behavior. Without this close interaction from mother, the ANS is negatively affected.

Other studies have shown that HF HRV is an important marker of parasympathetic activity (Hoffheimer, Wood, Porges, Pearson, Lawson, 1995). The literature suggests that newborns with good developmental outcomes often have high HF HRV, which signifies that HF HRV may be a major component of appropriate engagement with the environment (Hoffheimer, Wood, Porges, Pearson, Lawson, 1995).

Another study was done where researchers compared the HRV of infants with cyanotic versus acyanotic heart defects, as well as healthy infants (Aletti et al., 2012). The study included 15 children with CCHD, eight with cyanotic defects and seven with acyanotic defects, as well as 10 healthy children. The healthy study participants averaged 15 months of age and the participants with CCHD averaged between 20-28 months of

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

age, depending on type of defect. HRV was determined by examining three-minute RR interval segments from the data collection of each participant. The researchers found that healthy infants had higher HRV than infants with a congenital heart condition, but no significant difference between HRV in cyanotic versus acyanotic defects (Aletti et al., 2012).

HRV is a significant factor of child language competence and symbolic play during the third year of life (DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007). Researchers monitored fetal HRV from 20-38 weeks gestation and then continued with a two-year follow up evaluating the participants' mental and psychomotor development. There were significant links of these measures to fetal HRV; drawing the conclusion that autonomic nervous system function can have an impact on development in healthy infants (DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007).

This literature describes differences in ANS function in healthy and cardiac infants as well as relationships between early ANS function and later neurodevelopment. Identifying these relationships can help clinicians and researchers develop early interventions to enhance optimal ANS development. This could result in better neurodevelopmental outcomes, potentially leading to a better quality of life for children with CCHD (Siddiqui et al., 2015).

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Chapter III: Methods

Study Sample: Participants included four newborn infants, all born with different complex congenital heart defects that underwent cardiac surgery within the first 30 days of life. Eligible infants were: (a) newborn infants diagnosed with any CCHD either prenatally or after birth, (b) have at least one English speaking parent at least 18 years of age or legally emancipated, (c) be less than 30 days old at the time of data collection. Infant exclusion criteria was: (a) presence of co-existing, non-cardiac congenital defect or syndromes at the time of recruitment because of the potential independent effects on ANS function and (b) on-going cardiac pacing because HRV is calculated only on sinoatrial node-initiated complexes.

Study Design/Setting: Following informed consent, newborn health history was obtained from the medical record and included gestational age, birth weight, gender, type of feeding, type of cardiac defect, age at surgery, perioperative data, medications, concurrent diagnoses (e.g. gastroesophageal reflux, infections).

Measures: Twenty-four hour electrocardiographic (ECG) data were collected during hospitalization once before surgery and once five to seven days after surgery using the Bedmaster research tool linked to each bedside monitor and uploaded onto Dr. Harrison's MARS ambulatory ECG Analysis and Editing System (General Electric, Inc.). Each ECG complex was then identified and characterized with regard to morphology by the computer software using a pattern recognition method. Artifact was eliminated. This preliminary analysis was then over read and edited by Dr. Harrison to assure proper identification. Final calculations were based solely on normal sinoatrial node-initiated complexes. The Lomb-Scargle periodogram was used to calculate linear measures of

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

HRV. Power in three frequency domains was quantified and expressed in (ms²): very low frequency (VLF; 0-0.04Hz), low frequency: (LF; 0.04-0.3Hz), and high frequency (HF; 0.3-1.3Hz). VLF primarily been studied in adults and has been shown to represent parasympathetic activity (Tripathi, 2011). LF is a measure of both sympathetic and parasympathetic activity therefore is difficult to interpret. HF is an accepted measure of parasympathetic activity (Pumpria et al., 2002).

Non-linear measures provide further information that cannot be captured through linear HRV analysis. Poincare plots are a beat-to-beat interval analysis that allows examining of non-linear influences on the heart rate. The ratio of SD1 (width of the ellipse) to SD2 (length of the ellipse) is used to form the Poincare plots and is labeled SD12. SD12 provides information about sympathetic activity. Normal Poincare plots have an SD of greater than 0.15ms but less than 0.55ms. Poincare plots falling below 0.15ms are referred to as torpedo type plots and Poincare plots above 0.55ms are referred fan-shaped plots. Both are associated with higher levels of norepinephrine and risk of mortality in adults (Harrison & Brown, 2017).

Analysis Plan: Hourly HRV was examined graphically, descriptively, with t-tests, and with Mann-Whitney tests.

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Chapter IV: Results

Four infants, each with different types of CCHD, were included in this study. The types of CCHD were coarctation of the aorta, transposition of the great arteries, double-outlet right ventricle, and hypoplastic left heart syndrome. Table 1 presents the demographics of each infant including the diagnoses, infant birth weight, age in days when the infant had surgery and length of stay in the hospital.

All infants showed significant changes in HRV 1 week after surgery. VLF, LF, and HF HRV were all significantly higher in infants 1, 2, and 3, as shown in Table 2 and Figure 1. In contrast, VLF was not significantly different, and LF and HF were significantly lower in Infant 4 (diagnosed with hypoplastic left heart syndrome), shown in Table 2 and Figure 1.

Non-linear measures showed more abnormal Poincare plots post-operatively (11%-60%) than pre-operatively (0%-18%), revealing increased sympathetic activity following surgery in these infants (see Figure 2). The infant with hypoplastic left heart syndrome (Infant 4) showed the highest percentage of abnormal plots both pre- and post-operatively, 18% and 60%, respectively. Infant 1 showed 0% abnormal plots pre-surgery as opposed to 60% normal plots following surgery. Infant 2 displayed 5% abnormal plots before surgery compared to 25% abnormal plots post-surgery. Infant 3 displayed 0% abnormal plots pre-surgery compared to 11% abnormal plots post-surgery. SD12 was significantly different post-operatively only in Infant 4.

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Chapter V: Discussion and Conclusion

We examined linear and non-linear HRV measures pre-operatively and post-operatively in four infants with different types of CCHD. Three infants (diagnosed with coarctation of the aorta, transposition of the great arteries, and double-outlet right ventricle) demonstrated higher post-operative levels of linear HRV power compared with pre-operative levels, as well as fewer abnormal Poincare plots. These findings revealed differences in linear and non-linear HRV by cardiac defect.

Increased parasympathetic activity, demonstrated by increases in VLF and HF, suggests a better functioning autonomic nervous system in these infants after surgery. However, infant 4 showed a decrease in HF HRV, which may indicate a less well-functioning parasympathetic nervous system. It is possible that this reduction in ANS function is related to the severity of heart defect for this infant, who was born with hypoplastic left heart syndrome, one of the most serious heart defects in which infants undergo multiple surgical procedures (Hoffman, 2009). Additional studies with larger sample sizes and multiple longitudinal assessments are needed to enhance our understanding of relationships between specific cardiac defects and autonomic function. Knowledge about associations between early autonomic function and type of cardiac defect will assist with tailoring early interventions to optimize neurodevelopment in this vulnerable population.

Limitations

Differences in abnormal Poincare plots may have been related to variations in length and time of data collections. Some data was collected in the middle of the day, when sympathetic activity would be higher, whereas some data was collected throughout

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

the night, when you would expect the infant to be resting, thus less sympathetic activity.

More studies examining HRV for the same duration and at the same time each day is needed.

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

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ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

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ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

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ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Tables and GraphsTable 1: *Sample Demographics*

Infant	Diagnosis	Birth Wt (kg)	Sex	Age (days) at Surgery	Length of Stay (days)
1	Coarctation of the aorta	3.42	M	5	17
2	Transposition of the great arteries	4.00	M	10	17
3	Double-outlet right ventricle	2.72	M	5	17
4	Hypoplastic left heart syndrome	3.42	F	9	18

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

Table 2: *Linear HRV (power spectral density) Analysis*

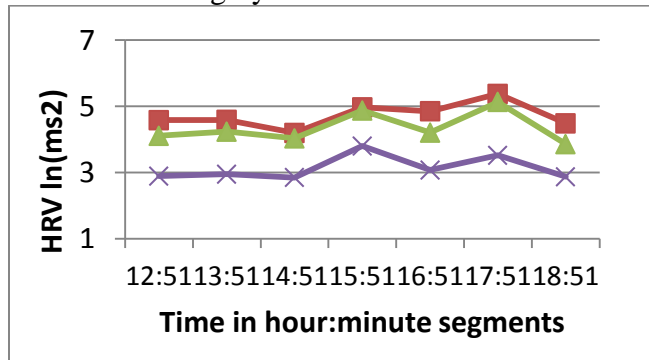
Infant		Pre-surgery					1 week after surgery					Comparisons ^a		
		obs	Mean	SD	Min	Max	obs	Mean	SD	Min	Max	<i>t</i> (Z)	<i>df</i>	<i>p</i>
1	VLF	82	4.37	0.9	2.01	7.03	44	5.65	0.8	2.4	7.16	-7.52	43	0.00
	LF	82	4.06	0.9	1.96	6.77	44	4.74	0.5	3.4	5.58	-6.04	43	0.00
	HF	82	2.94	0.5	1.04	5.67	44	3.29	0.4	2.7	4.25	-3.7	43	0.00
	LF/HF	82	1.4	0.4	0.7	3.47	44	1.45	0.2	1	1.75	-1.6	43	0.11
	SD12	8	0.25	0.1	0.16	0.43	5	0.16	0.1	0.1	0.27	(-1.48)		0.19
2	VLF	228	3.22	1.2	0	6.26	41	5.52	0.9	2.7	7.7	0	40	0.00
	LF	227	2.46	1	0	5.61	41	5.22	0.8	2.8	6.43	-17.86	40	0.00
	HF	222	2.87	0.5	1.6	5.23	41	3.58	0.4	3	4.54	-9.86	40	0.00
	LF/HF	222	0.84	0.4	-0	2.2	41	1.46	0.2	0.9	1.82	-10.3	40	0.00
	SD12	20	0.4	0.3	0.23	1.41	4	0.19	0	0.1	0.23	(-1.63)		0.25
3	VLF	80	4.38	0.9	1.9	6.21	90	5.41	0.9	2.8	6.93	-6.27	77	0.00
	LF	80	3.29	0.7	1.55	5	90	4.09	0.9	2.8	6.93	-7.15	77	0.00
	HF	80	3.12	0.5	2.55	4.36	90	3.98	0.6	2.7	5.79	-8.97	77	0.00
	LF/HF	80	1.07	0.2	0.47	1.45	90	1.03	0.1	0.6	1.46	1.27	77	0.21
	SD12	7	0.26	0.1	0.2	0.34	9	0.21	0.1	0.1	0.28	(-1.05)		0.34
4	VLF	188	5.22	1.1	1.99	7.37	114	5.14	1	2.6	7.79	0.14	107	0.89
	LF	188	5.06	0.7	2.8	6.8	114	4.92	0.9	2	8.24	2.88	107	0.01
	HF	188	3.8	0.5	2.56	7.18	114	3.39	0.6	2.5	6.26	6.99	107	0.00
	LF/HF	188	1.33	0.1	0.95	1.67	114	1.47	0.2	0.5	2.16	-4.35	107	0.00
	SD12	18	0.23	0.1	0.13	0.68	10	0.16	0.1	0.1	0.25	(-2.10)		0.04

Note. VLF = very low frequency, LF = low frequency, HF = high frequency, LF/HF = ratio of low to high frequency.

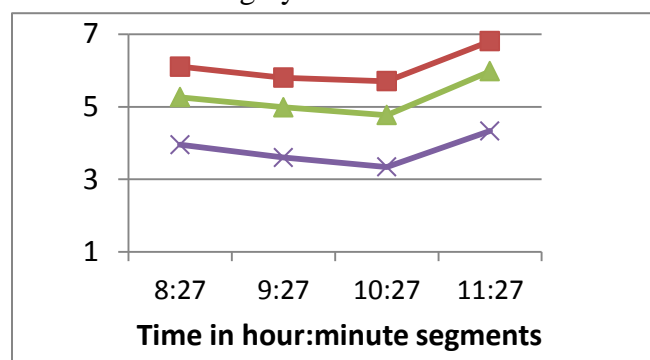
^at-tests or (Wilcoxon signed ranks)

ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

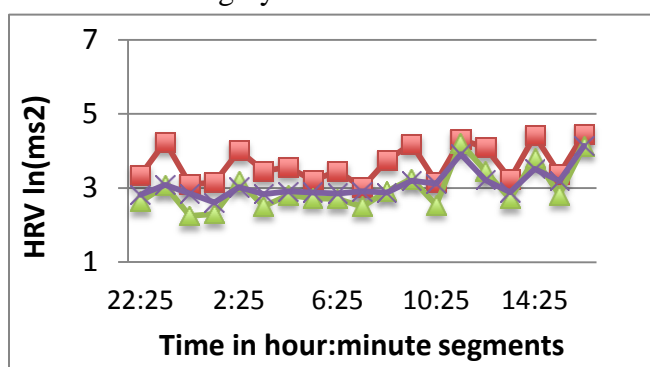
Infant 1: Pre-surgery



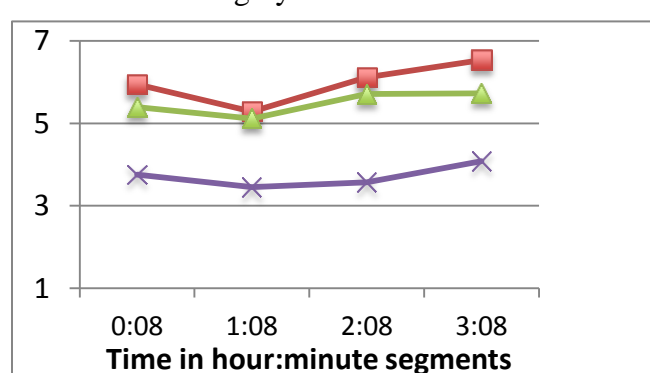
Infant 1: Post-Surgery



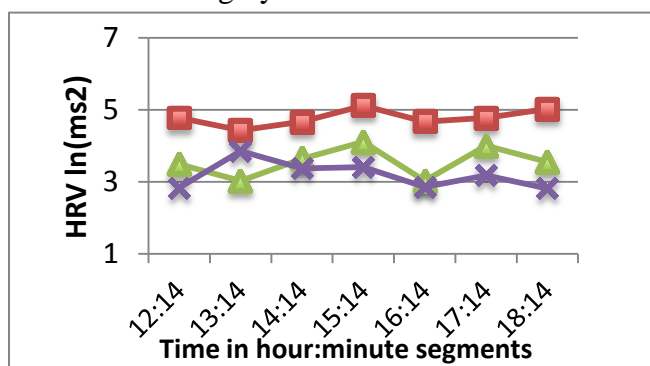
Infant 2: Pre-surgery



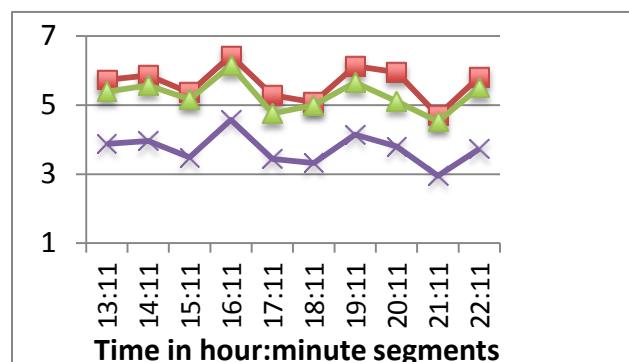
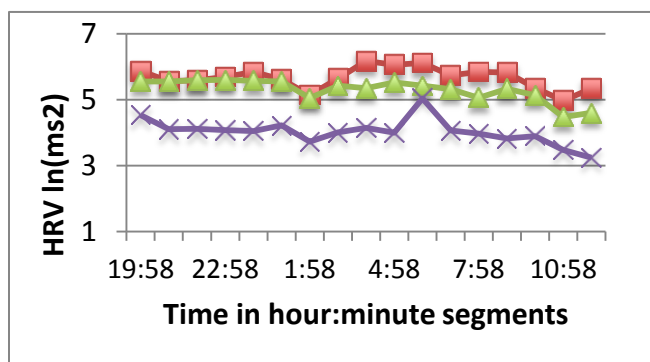
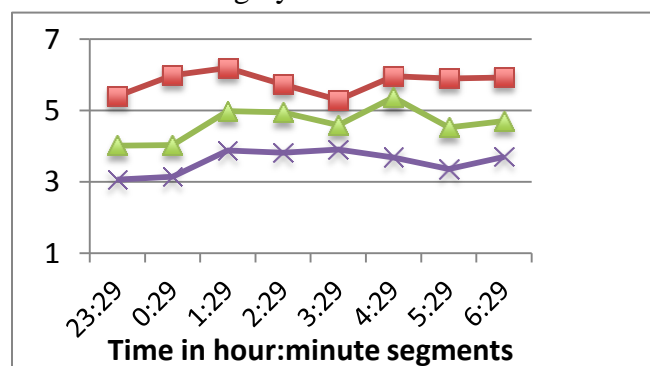
Infant 2: Post-surgery



Infant 3: Pre-surgery



Infant 3: Post-surgery

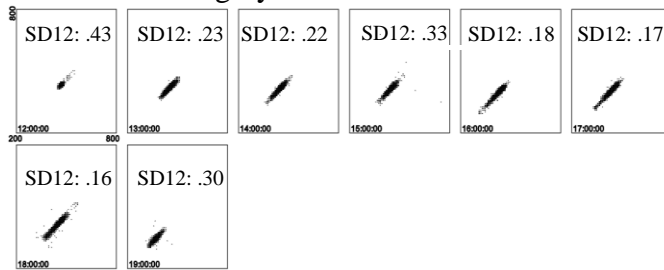


ANS FUNCTION IN NEWBORNS WITH CONGENITAL HEART DISEASE

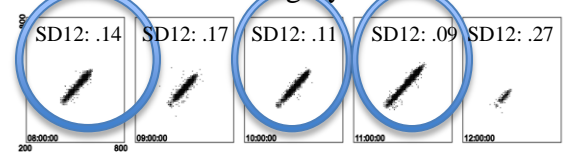
Figure 1: Linear HRV data collected from before surgery and post surgery. The red line represents very low frequency (VLF) HRV, a measure of parasympathetic activity. The purple line represents high frequency (HF) HRV, also a measure of parasympathetic activity. The green line represents low frequency (LF) HRV, a measure of sympathetic and parasympathetic activity, therefore, LF HRV is difficult to interpret, but VLF HRV and HF HRV can show the functioning of the autonomic nervous system.

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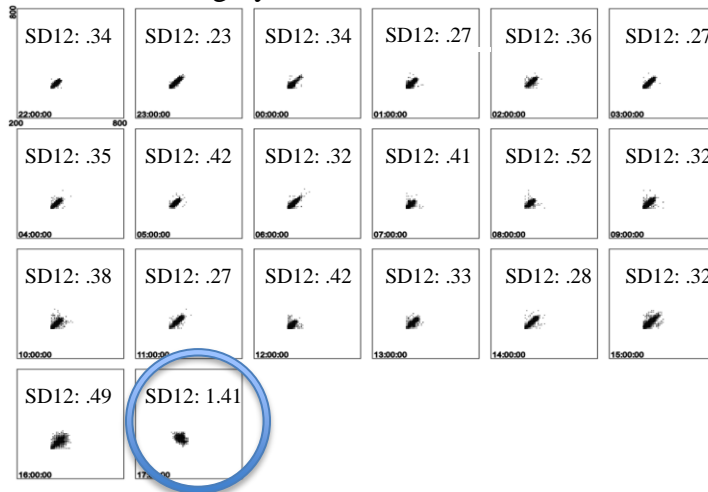
Infant 1: Pre-surgery



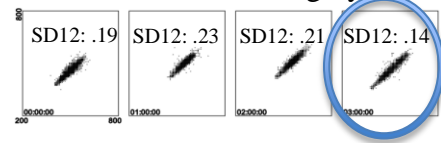
Infant 1: Post-surgery



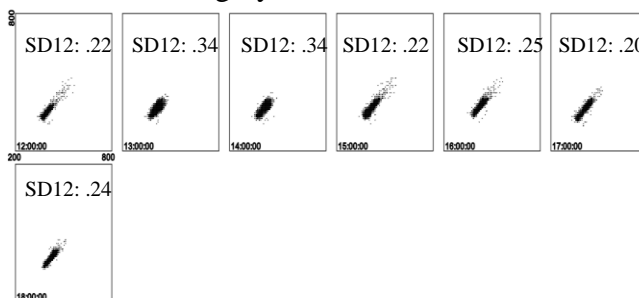
Infant 2: Pre surgery



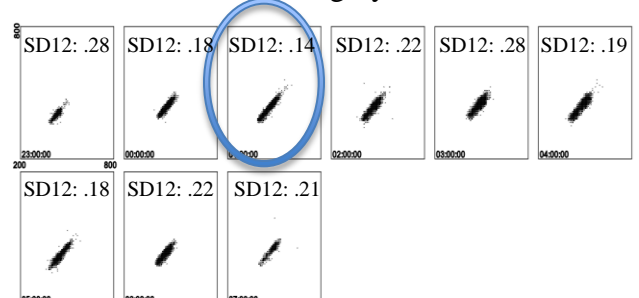
Infant 2: Post-surgery



Infant 3: Pre-surgery

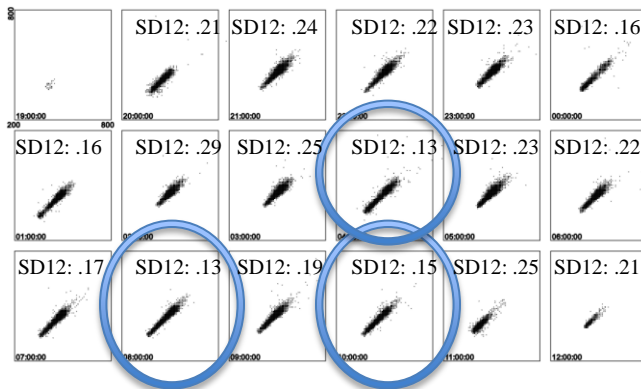


Infant 3: Post-surgery



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Infant 4: Pre-surgery



Infant 4: Post-surgery



Figure 2: Non-Linear HRV (Poincare Plots) display SD12 (the ratio of length to width). Each box represents an hour recording, and each point in the Poincare plot is an individual heartbeat. Normal plots display an SD12 value of .15-.45. Abnormal plots are circled.